First report of deep gene sequencing (DGS)in two patients with brain myeloid sarcoma.

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Background: Myeloid sarcoma (MS) is a rare extramedullary manifestation of acute leukemia (AL) occurring in 2-9% of patients. Primary MS involving the central nervous system (CNS-MS) is even rarer, described only in isolated case reports. Prognosis in these patients appears to be poor. Due to the rarity of cases, the cytogenetics and genomic landscape of MS is incompletely understood. Nonetheless, to elucidate the natural history, prognosis and treatment strategies for this deadly disease, the continued study and reporting of as many cases as possible remains the only reference and source of information for clinicians and patients facing this condition. We report here 2 cases of brain MS in which we conducted a comprehensive next generation sequencing (NGS) interrogating 406 genes by DNA sequencing and 265 genes by RNA sequencing (FoundationOne®HEME) implicated in hematological malignancies.

Cases and results of DGS: The examination of these two cases revealed the genomic alterations expected based on Acute Myeloid leukemia (AML) subtype for each case. In addition each case revealed variants of unknown significance with no common variants between the two cases. The first patient with APL, had a history of fibrosarcoma of the shoulder treated surgically in 2008 followed by a local relapse treated surgically in 2014 and with no evidence of relapse after surgery. Her APL had been treated initially in 2010. The phenotype of her MS in the brain in 2018 was similar to the one she had in the systemic APL in 2010. This time her bone marrow was free of disease. The second patient had a blast transformation of CML after several years of treatment with a second generation tyrosine kinase inhibitor. While the patient with CML in blast crisis succumbed to her disease. The patient with APL is currently undergoing re-induction with ATRA and ATO.

CML

APL

APL Myeloid Sarcoma

FLT3 D835Y

DNMT3A R882C

RARA PML-RARA fusion

Microsatellite Status Stable
Tumor Mutation Burden –LOW
3 Muts/Mb

Comprehensive next generation sequencing (NGS) of genes implicated in hematological malignancies:

406 genes by DNA sequencing.

265 genes by RNA sequencing.

CML Blast Crisis

ABL1 BCR-ABL1 fusion (p210)

IGH IGH-14q23 rearrangement

TP53 R337C

ASXL1 S577*

MMM2 Q1041*

Microsatellite Status Stable
Tumor Mutation Burden –
LOW
2 Muts/Mb

Conclusions:

To our knowledge this is the first report of DGS in brain MS. Neither case expressed Kit or Runx mutations previously described as common in non-CNS MS(Goldberg et al. Blood 2017. 130:2663). Both patients showed low tumor mutation burden and a stable microsatellite status suggesting low sensitivity to checkpoint immune inhibitors

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2. Cicconi L., Breccia M., Franceschini L., Latagliata R., Molica M., Rizzo M., et al. Prolonged arsenic trioxide (ATO) and All-Trans Retinoic acid (ATRA) Therapy for relapsed Acute Promyelocytic leukemia. Blood;2017130:147.